SCHOOL OF MEDICINE RESEARCH:

Targeting the Effects of Mass Radiation

BY RANDOLPH FILLMORE

April 26, 2006, marked the 20th anniversary of the nuclear accident at Chernobyl in the Ukraine. When a nuclear reactor exploded at 1:23 in the morning and burned, spewing radioactivity far and wide, authorities were unprepared to treat those individuals who had received lethal doses of radiation.

Many people did not realize they were in danger. Oral histories taken from survivors in ensuing years revealed that citizens living in the shadow of Chernobyl, and in the path of the deadly wind following the meltdown, had little to no knowledge of radiation hazards. Some sat on their rooftops, watching, awed, as the flames roared and the invisible, deadly rain poured down. In conflict still is the total number of the casualties who died from lethal doses of radiation in the hours, days, and weeks following the tragedy.

If a nuclear incident occurred in the United States, either by accident or design, how ready are we to deal with large numbers of severely radiated victims suffering acute radiation syndrome (ARS)? According to Thomas MacVittie, PhD, professor of radiation oncology at the School of Medicine, we are not ready—not by a long stretch.

Although Americans lived in fear of a nuclear attack during the Cold War, preparations for treating mass radiation casualties in the aftermath of a nuclear accident or attack are still lacking, even with post-Chernobyl knowledge.

"Chernobyl is a good example—from a treatment perspective—of a situation in which a large number of people survived lethal doses of radiation because of expert supportive care, despite the fact that victims were not properly treated with available appropriate therapeutics or mitigators," says MacVittie, principal investigator (PI) on a five-year, $46 million National Institute of Allergy and Infectious Disease (NIAID) grant aimed at clinical preparation for a nuclear incident.

According to MacVittie, supportive care in combination with available drugs is still the best treatment protocol available today. "Good supportive care—with fluids, antibiotics, nutritional support, and blood products—can save the lives of severely irradiated people," he explains. But MacVittie and his team, which includes experts from the University of Illinois-Chicago and Indiana University as well as from UMB, are exploring other treatment protocols for high numbers of casualties from a nuclear accident or attack.

Although treating radiation exposure is a complex public health issue with many unknown factors, the work funded by the largest research contract ever received by the School of Medicine is not aimed at evaluating threat scenarios, nor are investigators charged with devising public health logistical efforts necessary to treat victims.

For MacVittie and colleagues, the top priority is testing candidate medications that might prove useful in treating large numbers of severely irradiated patients with serious respiratory, gastrointestinal, and blood cell damage.

Today a nuclear attack is less likely to come from the warhead of an intercontinental ballistic missile, as was feared during the Cold War. A more likely scenario is the detonation of an improvised nuclear device (IND) by a terrorist.

MacVittie says, "We are not talking about a 'dirty bomb,'" a radiation dispersal device that would probably not be highly destructive, nor produce ARS. Rather, the mass casualty treatment scenario focuses on the detonation of a fairly large, perhaps one kiloton improvised nuclear device (the Hiroshima atomic bomb was 12 kilotons) that could produce a thousand or more moderately or severely radiated casualties.

According to MacVittie and a co-investigator Ann Farese, MS, research associate in the Department of Radiation Oncology, there is a great need for more practical approaches to protect the American public from the aftereffects of radiation from an IND. They point out, however, that there are currently no drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of lethally irradiated people. Treatment drugs could include drugs that are already approved for treating the aftereffects of chemotherapy, such as neupogen, uelasta, and interleukin-11, but the drugs must be approved by the FDA for such an application.

In the event of mass exposure to radiation, the first challenge would be sorting out the degree of victim exposure. Patients with Level I exposure could be treated as outpatients. Level II, moderate exposure, would require closer attention. Those irradiated at Level III would be considered severely irradiated and would have to be hospitalized. Level IV would involve victims who, without aggressive treatment, would succumb to fatal doses.

Symptoms of ARS include malaise, nausea, vomiting, and loss of consciousness. Those receiving severely high doses of radiation would suffer thrombocytopenia (low blood platelets) and granulocytopenia (low white blood cells) as the lethal doses of radiation shut down the production of these cells aimed at fighting infection and preventing bleeding. However, some victims could be rescued from both kinds of blood injury only to succumb to a fatal gastrointestinal (GI) crisis.

Severe radiation exposure would destroy cells in the GI tract, preventing the mucosal barrier from doing its job of screening out noxious bacteria and chemicals. The destruction would also prevent the stem cells that line the GI tract from carrying out their normal, three-day, total rejuvenation cycle. The hope would be, that with appropriate supportive care and new treatments to promote cell regrowth, the GI tract could be stabilized and regenerated toward normalcy.

"Those exposed to high doses of radiation can survive if fluids are replenished, antibiotics are given, electrolyte imbalances are restored, and the mucosal immune system is stabilized and recolonized with resistant flora," says Alessio Fasano, MD, pediatric gastroenterologist, director of the School of Medicine's Mucosal Biology Research Center, and co-PI on the NIAID grant. "Blood cells and platelets can be replenished by transfusion, but the function of the GI tract, particularly its barrier function, must be rebuilt by promoting cell growth—if patients are to survive."

Since there are no FDA-approved drugs for treating those lethally radiated, MacVittie's team is looking at current medications and determining how they can be better used. The blood-forming system, like the GI tract, must be similarly rebuilt using drugs that stimulate stem cells to renew themselves.

Existing drugs should be stockpiled, along with antibiotics such as Cipro®, for use in the event of an IND incident, suggests MacVittie. Furthermore, drugs already approved for use in the clinic to treat chemotherapy-induced myelosuppression (inhibition of the bone marrow's production of red blood cells, white blood cells, and platelets) and mucositis (inflammation of the lining of the mouth, throat, or GI tract) should be made available in all clinical treatment centers and hospitals. MacVittie also notes that there are no treatments for victims with both high irradiation levels and injuries, such as severe burns or other trauma.

Although treating mass casualties in the event of an IND incident is the impetus for the grant, finding better protocols for treating the medical needs of radiated cancer patients is a study application that could be applied to everyday clinical use, says MacVittie.

"The advantage with clinically administered radiation is we can control the dose," says MacVittie. "That's not the case with an IND of course. But what we learn about cellular regeneration and accelerating cellular growth in this study will have a profound effect on the treatment for patients receiving radiation and/or chemotherapy." □

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